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PATHOLOGICAL PHYSIOLOGY OF EXTREMAL STATES IN EXOGENIC INTOXICATIONS

S. N. Golikov

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16. Abstract
Data systematization on toxicological pathophysiology of exogenic intoxicators is attempted through modern concepts of mechanisms of action of poisons of varying origin with the goal of classification.

Characteristics, symptoms, syndromes, treatment and prevention are dealt with in addition to the extremal states of shock, collapse, coma and agony.

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PATHOLOGICAL PHYSIOLOGY OF EXTREMAL STATES IN EXOGENIC INTOXICATIONS

S. N. Golikov[1]

Like other factors which cause extremal states, poisons are extreme environmental stimuli. Attacking the organism in different ways (through the respiratory tract, cutaneous coverings, mucous membranes, gastrointestinal tract), they can cause serious damage, frequently threatening human life. /267*

In contrast to the damage produced by trauma, electric current, overheating and cooling, poisons at the time of action do not cause any visible injury, so that their entry into the organism remains unobserved (the only exceptions are irritating gases, burning fluids and other substances which cause local injury and deep destructive changes). Several poisons are characterized by a latent period of action during which the poisoning is not clinically evident.

Hence, poisons as harmful factors in the environment present great danger. It is no accident that some foreign toxicologists call them "the silent injury".

Poisons have been known since time immemorial, but their study began only at the end of the nineteenth century when the experimental method was introduced to medicine. The first experimental study of the pathophysiology of poisoning was a work by Bernard who studied the mechanism of action of curare. In Russia, the first work on toxicology was done by Ye. V. Pelikan. Toxicology began to develop particularly intensively following the First World War, which demonstrated the powerlessness of medicine in the face of terrible chemical weapons (the number of victims of toxic agents was about 1.3 million; mortality varied from 10 to 30%). During the last hundred years, toxicology has become an independent scientific discipline, based on modern methods of investigation. The successes achieved by toxicology in establishing the mechanism of action of many poisons, working out methods of treatment, prevention of poisoning and so forth are indisputable. A great debt in connection with the development of Soviet toxicology is owed to N. A. Soshestvenskiy,

*Numbers in the margin indicate pagination in the foreign text.

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A. A. Likhachev, S. V. Anichkov, N. N. Sabitskiy, N. V. Lazarev, V. A. Sanotskiy, A. I. Cherkes, Yu. V. Drugov, and others, thanks to whose efforts toxicology has come to occupy a distinguished place among the medical and biological sciences in the Soviet Union. In the course of development of these problems, a general /268 tendency has gradually come to light — finding that characteristic or specific feature which distinguishes one poison from another and establishing the point at which its action is directed against the organism; to find the differential--diagnostic principles.

Considerably less attention has been devoted to the pathophysiological aspect of poisoning: determination of the general features of the action of poisons as extreme environmental stimuli. This is particularly true of the extremely serious symptoms of poisoning, which we refer to as extremal states. If we do not take into account the individual recommendations having to do with the treatment of serious poisoning, contained in handbooks, we could say that there are no systematized data in the literature on the pathophysiology of extremal states, produced by numerous poisons. In addition, it is precisely this dichotomy in the practical respect which is particularly important. In fact, one of the most complicated and difficult-to-solve problems in clinical toxicology is the treatment of serious forms of poisoning, bordering on terminal states.

In the present chapter, an attempt has been made to systematize the data on the pathophysiology of extremal states in poisoning victims, taking into account modern concepts of the mechanism of action of poisons of different origins. This problem has proved to be quite complex. Difficulties were encountered in particular in conjunction with the abundance of poisons which have different mechanisms of physiological action. This situation is made even more serious by the lack of a uniform generally accepted pathogenetic classification of poisons. No clinical classification of poisons has been worked out, although there are sufficient detailed descriptions of the symptoms of poisoning by various poisons. These data, particularly the attempt to isolate syndromes, characterizing the clinical manifestations of poisoning, are of great practical value. However, usually they are of a descriptive nature; they contain insufficient data on the origin of the symptoms observed and of the possible

biochemical mechanisms which form the basis of the toxic action of the substance. In addition, all of these reports are scattered through a number of literature sources.

We by no means believe that we could fill in this gap even partially within the scope of a single chapter. This chapter should be viewed only as a first step in dealing with problems of modern toxicology from the standpoint of the problem posed in the book — the pathophysiology of extremal states.

Brief Characteristics of Poisons

There are numerous chemical substances which under the appropriate conditions can cause poisoning. These include numerous industrial poisons, poisonous chemicals used in agriculture and in the home, substances of natural origin (vegetable and animal), various medicinal substances (many of which cause poisoning in toxic doses) and so on. A particular group of poisons is constituted by poisoning substances.

The danger of development of poisoning is determined not only by the toxicity of the substance but a number of other factors, among which the availability of the substance is primary. Thus, serious poisonings with alcohol are encountered rather frequently, although alcohol by reason of its toxicity could be included among the less toxic compounds. Statistics indicate that cases of poisoning occupy one of the leading places in diseases associated with the damaging effects of ecvironmental factors. According to the data of the American Association of Centers for Combating Poisoning, more than one million cases of poisoning are recorded in the United States each year, of which eight thousand have a lethal outcome (Comstock, 1968). The catastrophic scope of an "epidemic" of poisoning stimulated the Congress of the United States to pass a presidential resolution declaring the third week of March to be National Poisoning Prevention Week. The frequency of poisoning by various substances can be judged on the basis of data presented by MacEachen, Crawlord et al. (1968).

Total Poisons	27,033
Breakdown as follows:	
Analgesics, febrifuges and anti-inflammatory substances	7,313
Neurotropic substances	3,465

Washing agents	3,292
Medicinal substances affecting the digestive function	1,190
Dyes and organic solvents	1,095
Cosmetics	1,091
Foods, including alcohol	1,084
Substances influencing the respiratory function	1,030
Pesticides	961
Other substances	6,512

Here the data presented come primarily from the area of domestic poisoning. A special group is constituted by cases of acute industrial poisoning, caused by such dangerous substances as poisonous gases and vapors, caustic acids and alkalis, solvents, nitrogen compounds, mercury, arsenic and many other poisonous substances. Even more dangerous are the poisonings by modern toxic agents (zarin, zoman, V-gases) and certain "old" substances used for chemical attack (phosgene, yprite, prussic acid and so forth). The study of the biological effects of different toxic agents was embodied in a great many papers especially those by foreign authors. Detailed information on this is presented in the numerous handbooks on the subject.

The existing classifications differentiate poisons on the basis of their origin, use, toxicity, and membership in a given group of pharmacological substances (if we are speaking of medicines). There is no uniform pathogenetic classification of poisons. Attempts at classification of poisons on the basis of pathogenetic features encounter considerable difficulties associated with the fact that the biologically active substances in toxic doses have a multifaceted influence on the organism (as the result of both direct and indirect action on various organs and functional systems). Nevertheless, by a careful study of the effect of poisons on the animal organism, one can see the most characteristic clinical phenomena (syndromes) of poisonings by a given substance (or group of substances). Clinically, one can distinguish between asphyxiating, irritating (burning), skin-abscessing, narcotic, spastic, blood, heart, vascular (capillary), renal, hepatic, psychomimetic and other poisons.

Pathophysiological analysis makes it possible to talk about the hypoxic poisons with different types of action; the poisons with a primarily central or peripheral action; substances which selectively intervene in cholinergic

and adrenergic transmission (synaptic, mediator poisons); substances which act primarily on the coagulatory system of the blood and so on. A biochemical study of the mechanism of action of poisons makes it possible to isolate several groups of substances as a function of the selective influence on the enzyme systems of the organism (A. A. Pokrovskiy, 1961). /270

Within the framework of the current chapter, it would be hardly possible to go into a deep discussion of the thorny and far from solved problems of classification of poisons. There is something else which must be clarified. No matter how diverse the effect of poisons seems to us and no matter what attempts we may undertake to classify them as a function of various characteristics inherent in them, in the course of the pathological process (poisoning) a moment comes when the action of the poison, so to speak, takes a back seat and pathophysiological mechanisms begin to dominate which are common to a given extremal state regardless of the nature of the harmful factor. In this sense, a poison is a distinctive triggering mechanism of a complex chain of pathophysiological changes. Of course, one cannot discard such ideas as the one that the nature of the poison leaves a characteristic imprint on the course of the pathological process. In a further examination of the pathophysiology of extremal states which arise during poisonings, we have attempted to take into account on the one hand the selectivity in the action of poisons and on the other the pathogenetic communality of the functional changes that occurred during it.

Extremal States During Poisoning

Any poisonous (strongly acting) substance under certain conditions (size of dose, method of administration, state of the organism) can cause serious poisoning with a lethal outcome. In the course of acute poisoning, it is natural to distinguish a preterminal period, characterizing sharp inhibition of the most important vital functions of the organism (respiration, circulation, neurohumoral regulation). The preterminal phase of poisoning is viewed as an extreme, scarcely tolerable (extremal) state whose duration may vary according to of a number of factors (dose of poison taken into the organism, pathogenetic mechanism of its action, tolerance of the organism for a given poison, age and sex of the victim and so on).

We can distinguish the following basic forms of extremal states encountered in poisoning: shock, collapse, coma, agony. Numerous extremal states have all of the extreme symptoms of intoxication, but they do not disclose the pathogenetic mechanisms of their development under different chemical effects. Thus, as the basis of shock in toxic effects, there may be such factors as chemical burns, anaphylaxia, and hemolysis. Still more diverse mechanisms complicate the development of collapse (hypoxia, paresis of the capillaries, cardiac weakness, pulmonary edema and so forth). This also applies to other extremal states. At the same time, each of these factors has its own genesis depending on what poison or group of substances causes it (Table 24).

Shock.

Shock arises in the case of extensive chemical injuries to the skin and the mucous membranes of the respiratory and gastrointestinal tract. According to the current classification, shock with such chemical injuries must be included among burn shock, which in turn is a variety of pain shock. In this case, a chemical substance plays the role of an extreme stimulus, in response to which sharp disturbances of the nervous regulation of vital processes occur /272 (serious disturbances of hemodynamics, respiration and metabolism).

TABLE 24. EXTREMAL STATES IN POISONINGS

State	Toxic Agents	Pathogenesis
Shock		
General reaction of the organism to a serious chemical injury, accompanied by profound disturbances of nervous regulation of vital activity (disturbances of hemodynamics, respiratory function and metabolism). In poisonings, there may be painful and humoshock (hemolytic and anaphylactic).	Strong acids, alkalis, burning gases and vapors, toxic agents with a skin abscessing effect. Bichloride of mercury and other nephrotoxic substances. Hemolytic poisons. Distilled water when given intravenously. Poisons of a protein nature, vegetable and animal origin. Some medicinal substances. Histamine.	Massive chemical injury accompanied by sharply pronounced painful syndrome, playing the role of shock factor (pain shock). Intensive disturbance of erythrocytes accompanied by formation in the organism of toxic products which play the role of a humoral shock inducing factor (hemolytic shock). The poison is antigen; it causes an extreme degree of allergic reaction (anaphylactic shock).

TABLE 24 (CONTINUED)

State	Toxic Agents	Pathogenesis
Collapse		
Acute cardiovascular insufficiency, leading to circulatory hypoxemia and hypoxia of the brain. Characterized by profound inhibition of the central nervous system, a sharp drop in the arterial and venous pressure, a decrease in the mass of circulating blood and disruption of metabolism. In the case of poisonings, it usually develops in the form of an independent syndrome, while in some cases it develops in the torpid phase of shock.	Cardiac and vascular poisons, substances which cause hypoxia of various types, narcotics in large doses.	As the result of direct administration of poisons on various elements of the cardiovascular system, paralysis of the vasomotor center develops (under the influence of large doses of neurotropic substances), the heart (cardiac poisons) or capillaries (capillary poisons). A reflex mechanism for the development of collapse under the influence of chemical burns and serious disruption of the function of various organs and systems.
Coma		
A state of acute inhibition of higher nervous activity, expressed by deep clouding of the consciousness, disruption of the function of all analyzers and internal organs.	Narcots, neuroleptics, hepatotropic nephrotoxic substances; poisons causing hypoxia and acute changes in water-ion balance.	The basis of the development of coma is a sharp drop in the brain metabolism as the result either of direct inhibitory effect of poison on the higher functions of the brain (narcotics, neuroleptics) or endogenic humoral influences caused by the harmful action of a poison upon various organs and systems (in conjunction with which one can distinguish liver, kidney, hypoglycemic coma and other varieties of comatose states). One

TABLE 24 (CONTINUED)

State	Toxic Agents	Pathogenesis
		of the partial reasons for the exogenic toxic coma is anoxia, which accompanies many poisonings (in serious cases). In addition, in its origin there may be disturbances of water-ion balance and B_1, B_2 vitamin insufficiency.
Agony		
Inhibition of basic vital processes, preceding the onset of clinical death.	All poisons.	Profound disturbance of activity of higher regulating centers of the cerebral cortex and irritation of the bulbar and spinal cord centers characterizing the latter reactive and accommodative changes in the functions of the organism. Depending on the nature of the preceding extremal state, (shock, collapse, coma) and the conditions of poisoning (poison, dose, aggregate state) the agonal state may last from several minutes to several hours.

In man, increased sensitivity is observed to certain medicinal substances which sometimes take the form of serious disturbances (agranulocytosis, thrombocytopenic purpura, hemolytic reactions, acute icteric atrophy of the liver, exfoliative dermatitis, encephalopathy, bronchospasm, allergic angiopathies). An extreme and very acute phenomenon of these reactions is anaphylactic shock. Salicylates, quinine, nitrites, antispasmodic preparations /273
(diphenine, hexamidine), sulfanilamides, antibiotics — this is far from a complete list of the substances which cause allergic reactions under the

appropriate circumstances. These reactions are produced by the formation of antibodies, with the medicinal preparation playing the role of antigen. The medicinal allergic reactions are similar to the anaphylactic reactions to foreign proteins in man (anaphylactic shock, urticaria, bronchial asthma, angioneuronal edema). They are linked to the endogenic liberation of histamine; it is possible that histamine is responsible for the characteristics of the clinical course of certain allergic reactions to medicinal substances (Lecomte, 1956; Rocha, E. Silva, 1955). The existence of such a mechanism is supported by the effectiveness of antihistaminic preparations not only in the exogenic histamine shock, but also in allergic reactions caused by other medicinal substances.

In cases of poisoning by certain poisons (bile, chromic and acetic acid, lead, arsenic, hydrogen arsenide, hydrogen sulfide, phenylhydrazine, toluene, nitrobenzene, paranitroaniline, etc.) hemolysis develops. However, hemolytic shock is rarely observed in conjunction with gradual and not instantaneous disruption of erythrocytes. A particularly rapid intracellular hemolysis can be caused by inhalation of pollen of certain bean plants *(Vicia fava)* during its fluorescent period. Usually cases of favism are found in Southern Italy among certain families, linked with a genetic deficiency of the enzyme glucoso-6--phosphate dehydrogenase. This state causes disruption of the balance between the erythrocytolytic enzyme and a factor which inhibits such lysis; as the result, hemolysis develops. Increased breakdown of erythrocytes is caused by substances that disturb their osmotic equilibrium: Berthollet's fluid, distilled water (when administered intravenously). The latter causes typical hemolytic shock.

Collapse.

Acute cardiovascular insufficiency, leading to circulatory hypoxemia. The pathogenesis of toxic collapse is largely related to selectivity in the action of poisons on various branches of the cardiovascular system. Its basis may be primary paralysis of the vasomotor center, paralysis of the heart (vascular system and myocardium) or paresis of the capillaries (a sharp drop in vascular tone). In addition, it is possible to have a reflex mechanism for the development of collapse under the influence of chemical burns and acute

disruption of the function of various organs and systems. The terminal phase of shock is characterized by collapse.

Acute cardiac insufficiency of circulation may be produced by the following: 1) acute bradycardia; 2) ventricular arrest due to pathological reflexes from the carotid sinus; 3) ventricular fibrillation; 4) paroxysmal tachycardia. Such disturbances are particularly characteristic of the toxic action of cardiac glycosides (preparations of digitalis, strophantine) and aconitine. Adrenalin in toxic doses causes ventricular fibrillation; acetylcholine and other cholinergics produce bradycardia. Capillary paresis is observed under the influence of histamine, poisons of the arsenic group and certain other compounds.

In order to demonstrate the role of the cardial factor in the development of collapse in cases of poisoning by certain substances, let us dwell in somewhat more detail on the pathogenesis of poisoning by cardiac glycosides. The first symptom of poisoning is a sharp reduction of the pulse, caused by irritation of the centers of the vagus nerves. Then the infrequent pulse is /274
suddenly replaced by a rapid one due to the direct irritating action of glycosides on the pacemaker of the heart. Soon an irregular rhythm interrupted by ventricular extrasystoles develops (blockage of the bundle of His). An extreme manifestation of disturbances of cardiac automatism is ventricular fibrillation and cessation of their inhibitory function (F. Shvets, 1963). The collaptoid state then observed is a direct consequence of acute cardiac insufficiency, leading to interruption of circulation of the blood. Primary paralysis of the vasomotor center can also cause acute circulatory insufficiency. It develops in cases of poisoning by large doses of cyanides and certain other substances. The differences described in the genesis of acute circulatory insufficiency, linked to the point of application of the action of the poison, helps to understand correctly the possible pathophysiological mechanisms of toxic collapse. However, in clinical practice it is usually difficult to isolate such components of the action of a poison which are linked either only with its central or its peripheral effect. Thus, at the basis of collapse observed under the resorptive effect of yprite lies its toxic influence on the vasomotor center, disturbance of the activity of the

heart and the paralytic action on the vessels (A. I. Cherkes, 1943). This view has been supported even more by the fact that acute cardiac insufficiency rapidly leads to hypoxia, which sometimes in turn intensifies problems with circulation. Hypoxia can also be of distinctive importance in the origin of disturbances in circulation. It is also necessary to take into account the possibility of action not of the poison itself but of the products of its hydrolysis in the organism. In addition, the acute destructive changes that occur in poisoning by various substances in individual organs and tissues, accompanied by the excretion of toxic products of breakdown, can have an influence on the vascular tone and on the permeability of the latter.

Coma.

Coma is a state of inhibition of the higher nervous activity, expressed by profound loss of consciousness, disturbances of functions of all analyzers — respiratory, skin, visual, auditory, defensive — and the internal organs.

In accordance with the proposed classifications, comatose states produced by poisons can be included among the exotoxic comas. N. K. Bogolepov (1951, 1962), among exotoxic comas, distinguishes comatose states caused by poisonous mushrooms, alcohol, medicinal substances (pharmacological comas), industrial poisons and carbon monoxide. The etiological principle is used as the basis for this classification.

The pathophysiological classification distinguishes between the following exotoxic comas: narcotic, anoxic, hypoglycemic, encephalopathic and spastic, as well as those comas which arise as the consequence of disturbances of water and ion balance (Gaultier, Fourhier, Mellerio, 1966). Clinicians, in addition, distinguish hepatic and renal (exotoxic) coma. We have attempted to systematize the small amount of data on comatose states from poisoning (Table 25).

In order to characterize the comatose states observed during serious poisonings, together with the data presented in Table 28, there are biochemical parameters which are significant. In certain comatose states of this kind there are significant changes in the brain metabolism, characterized primarily by a decrease in the intensity of respiration of brain tissue by 25% or more (in

narcotic, anoxic and hypoglycemic coma). In addition, there are changes in the level of phosphocreatine and inorganic phosphates and lactic acid. In narcotic coma there is a decrease in the level of lactic acid, indicating suppression of /276 reactions supplying energy. At the same time there is an accumulation of phosphocreatine and a decrease in inorganic phosphate. In anoxic coma there is opposite changes: a decrease in the phosphocreatine level, a rise in the lactic acid level and the level of inorganic phosphates. In hypoglycemic coma, the level of phosphocreatine decreases while that of inorganic phosphates increases. Important diagnostic significance can also be attributed to the morphological changes in the brain in certain comatose states (symmetrical foci of necrosis in carbon monoxide coma) (A. M. Grinshteyn, N. A. Popova, 1928).

TABLE 25. COMATOSE STATES IN POISONING

Coma	Toxic Agents	Characteristics of the Course of the Coma
Narcotic	Narcotics, soporifics, neuroleptics: chloroform, ether, alcohol, barbiturates, morphine, aminazine, etc.	Inhibition of central nervous system as the result of blockage of the synaptic transmission of signals. Barbiturates, in contrast to volatile anesthetics, do not cause analgesia during the initial stage. In alcohol coma — psychomotor irritation. Sedatives (meprobamate) and neuroleptics)(aminazine) cause "quiet" coma. Morphine coma is characterized by miosis and profound inhibition of respiration, relieved by allylnormorphine.
Anoxic	Hemolytic poisons: hydrogen arsenide, phenylhydrazene, snake venom, lead compounds, nitrogen compounds, benzene and so forth. Carboxyhemoglobin--forming poisons: carbon monoxide. Metahemoglobin-forming poisons: nitrites. Histotoxic poisons: prussic acid and its salts.	Anoxia due to a decrease in the amount of hemoglobin (hemolytic poisons), its conversion into the inactive form (carboxyhemoglobin, metahemoglobin) and as the result of paralysis of tissue respiration (cyanide). "Shock" coma is characterized by spasms, pink color of the mucous membranes; in the case of coma caused by hydrogen aresnide and other hemolytic poisons, there is hemoglobinuria, jaundice combined with cyanosis ("Indian skin"), uremia

TABLE 25 (CONTINUED)

Coma	Toxic Agents	Characteristics of the Course of the Coma
		(in the terminal phase). In cases of poisoning by hydrogen sulfide, coma takes place, of the "carbon monoxide" type. In coma which is produced by cyanides there is a bright pink coloration of the skin and mucous membranes, preceded by development of dyspnea, with rapid fatal outcome.
Hypoglycemia	Insulin,	Comatose state with muscular hypertension, tonic spasms and vegetative disturbances (with a predominance of parasympathicotonic symptoms). The coma is relieved by intravenous administration of glucose.
Coma with prolonged encephalopathies	Arsenic compounds, compounds of heavy metals, tetraethyl lead	The coma develops against a background of prolonged toxic encephalopathies. They are characterized by cephalitis, spasms, and fever. Coma may be eliminated or relieved by dithiols (BAL, unithiol).
Coma with disturbance of ion balance	Salts of bromine and magnesium	Basis is disturbance of ion balance. Bromine salts extract chlorine compounds and disturb ion equilibrium. If the level of replacement exceeds 2/5 coma will develop. Coma is reversible under the influence of chlorides. Magnesium salts combine with calcium compounds and disturb the ion balance. This causes a disruption of the permeability of the membranes. Coma resembles that of the narcotic type.
Hepatic coma	Trinitrotoluene, dinitrophenol, dichloroethane, carbon tetrachloride, atophane, para-aminosalicylic acid and other hepatotropic substances	Acute autointoxication due to elimination of the functions of the liver (hepatargia) as the result of acute toxic effects. Characteristics of the coma:

TABLE 25 (CONTINUED)

Coma	Toxic Agents	Characteristics of the Course of the Coma
		initial psychic irritation, hypothermia, hemorrhage, tremor of the extremities.
Uremic coma	Heavy metals: mercury, lead, bismuth, uranium, chromium, gold, arsenic; antifreeze, acetic acid and so forth	Acute renal insufficiency. Uremia. Characteristic ammonia smell of expired air, myosis, myoclonic twitches, hemorrhagic diatheses, hypothermia, azotemia, increased creatinine content in the blood and increased indicane content in the blood. Triad: exhaustion, edema, diarrhea.

Shock, collapse, coma and agony are the extreme manifestations of the action of an extremal factor. As a rule, their development is preceded by significant pathophysiological changes that indicate a predominant injury by the poison to a given functional system (systems). These states (poisoning syndromes) usually are distinguished on the basis of their clinical symptoms (the primary symptoms of poisoning). However a pathogenetic sense is incorporated in the term syndrome which has great significance for the pathophysiological classification of serious (pre-extremal) disturbances caused by poisons of different kinds. There is no strict classification of this kind. Hence, we have used Table 29 to describe the most important syndromes of poisoning in alphabetical order.

Clinical Symptoms of the Action of Poisons (Syndromes of Poisoning)

The clinical aspects of poisoning are one of the most fully studied problems in toxicology. However, this is true of poisonings only by comparatively few, most frequently encountered and accessible poisons. According to the data on the treatment of poisonings at the N. V. Sklifosovskiy Institute (Moscow), these poisons include carbon monoxide, dichloroethane, acetic essence and acids, phosphoorganic compounds (A. V. Margolin, V. N. Dagayev, 1968) as well as certain medications (soporifics, preparations of belladonna and

pachycarpine). Particular interest in conjunction with the development of the problem of the pathophysiology of extremal states in poisoning attaches to the /279
attempt that isolating the syndromes of poisoning. On the basis of the considerable experience gained in the treatment of acute poisoning, P. L. Sukhinin and Ye. A. Luzhnikov (1968) consider the following basic syndromes of disturbance to vital functions: 1) the syndrome of disturbance of respiration; 2) the syndrome of disturbance of hemodynamics; 3) acute renal insufficiency; 4) acute renal insufficiency. Let us pause briefly to study the characteristics.

TABLE 26. SYNDROMES IN POISONING

Adaptation syndrome	Combination of nonspecific manifestations arising in the organism under the influence of poisonous substances and capable of promoting the recovery of the disturbed equilibrium and increasing the resistance of the organism. Develops under the influence of any poison.
Apoplexic syndrome	Observed as an expression of the "lightning" form of poisoning by certain poisons in very large doses.
Allergic syndrome (iatrogenic disease)	Various allergic reactions in the form of anaphylactic shock, angioneurotic disturbances, bronchial asthma (acute form) and serum pain (inhibited type). Most frequent allergins — iodine, bromine, antibiotics, salicylates.
Asphyxia	Asthma arises as the result of acute insufficiency in the organism of oxygen. Caused by poisons which inhibit the respiratory center (morphine), preventing the activity of respiratory muscles (curare), disturbing the respiratory function of the blood (carbon monoxide, nitrites), and the activity of tissue respiratory enzymes (cyanides, hydrogen sulfide). Edema of the larynx (irritating gases and vapors), bronchiospasm (vegetative poisons), pulmonary edema (phosgene, nitrous oxide) also can cause asthma.
Pain syndrome	Emotional reaction of the organism to irritating action on the skin and mucous membranes of the respiratory and gastrointestinal tract, caused by chemical burns (strong acids and alkalis, irritating gases and vapors). In cases of poisoning with bichloride of mercury intestinal colic, which can take the form of a cause of shock.

TABLE 26 (CONTINUED)

Bronchiospasm	Bronchiospasm (asthmatic syndrome) arises in the cases of poisoning by cholinergic irritating substances (acetylcholine, muscarine, physostigmine and phospho-organic poisons). In certain cases, accompanied by laryngospasm. Under the influence of high concentrations of irritating gases and poisons, edema of the larynx may develop.
Hypotonia	Drop in arterial pressure may occur instantaneously. In these cases, it is one of the symptoms of acute cardiovascular insufficiency, which arise in cases of poisoning by cardiac glycosides, adrenaline, nitrogen compounds, dichloroethane and other poisons. In cases of poisoning with aniline, arsenic compounds, mercury, lead, organophosphoric poisons and the like, hypotonia is one of the constant and leading symptoms.
Hepatargia	Syndrome of insufficiency of liver function. Characteristic of poisoning by so-called liver poisons (dichloroethane, carbon tetrachloride).
Hypoxia	Oxygen insufficiency leading to asphyxia in serious cases. In addition to the factors which cause asphyxia, it is necessary to take into account the possibility of the occurrence of hypoxia due to cardiovascular insufficiency (circulatory type) and problems of external respiration (irritation of the lungs).
Hepatorenal syndrome	Insufficiency of the liver and kidneys due to their toxic injury.
Collapse	See Insufficiency of Circulation of the Blood.
Coma	See Clouding of Consciousness.
Myasthenia	Weakening of the transversely striated musculature due to suppression of the neuromuscular conductivity (curare and curare-like substances, cobra venom). In cases of blockage of transmission in the respiratory muscles — asphyxia.
Acute renal insufficiency (nephrotoxic syndrome)	Acute renal insufficiency develops in cases of poisoning by heavy metals (mercury, bismuth, lead, uranium), carbon tetrachloride and other substances. Acute renal insufficiency causes uremia.

TABLE (CONTINUED)

Acute psychotoxic state	Disturbance of psychic aspects with predominance of symptoms of crepuscular state, amentia, hallucinoses (delirium), catatonic disturbances. Observed in cases of exposure to psychomimetic substances, carbon monoxide, alcohol, tetraethyllead, bulbocapnine (catatonia) and so forth.
Pulmonary edema	Develops in the cases of poisoning by toxic agents (chlorine, phosgene) and caustic gases and vapors (nitrous oxide, ammonia) as well as in allergy, injuries to the kidneys, cardiac insufficiency, anemia, narcotic coma and other states caused by the action of poisons.
Parasympathetic syndrome	Symptoms of acute irritation of the parasympathetic (cholinergic) level of the vegetative nervous system (bradycardia, salivation, bronchospasm and bronchorea, sweating, myosis, hyperperistalsis). Caused by parasympathicotropic (cholinergic) poisons.
Clouding of consciousness	Depending on the degree of poisoning, characterized by syncope, amentia, deafness, drowziness and coma. Most frequently observed in cases of poisoning by narcotics and other substances with an inhibitory type of action on the central nervous system.
Spasm (extrapyramidal) syndrome	In cases of poisoning there may be clonic (corazole, cicutoxin, clonic-tonic (physostigmine, organophosphoric poisons) and tonic (strychnine) spasms. In cases of poisoning by anticholinesterase poisons the general spasms are preceded by intensive myofibrillations.
Syndrome of skin injury	Caused by various changes in the skin from superficial dermatitis to necroses of various degrees (caustic fluids, skin-abscessing toxic agents such as yprite, lewisite and the like).
Irritation of the eyes	Characteristic manifestation of the syndrome is pain in the eyes, blepharospasm, lacrymation, conjunctivitis of varying degrees of severity. Caused by irritating gases and vapors. Particularly strong influence by toxic agents on the lacrymatory effect (lacrymators).

TABLE 26 (CONTINUED)

Irritation of the upper respiratory tract	Irritation of the upper respiratory tract caused by painful sensations and catarrhal phenomena along the respiratory tract. Produced by irritating gases and vapors. The sternutatory toxic agents have a particularly strong effect.
Circulatory insufficiency	Insufficiency of circulation arises as the result of toxic influences on the heart (cardiac glycosides, aconitine, adrenaline) or vessels (vascular poisons). The extreme manifestation of this state is acute cardiovascular insufficiency (collapse).
Uremia	Self-poisoning of the organism as the result of insufficient renal function.
Shock	Extreme state of pain syndrome, anaphylaxia and hemolysis.

1. Syndrome of disturbance of respiration most frequently observed: a) in a comatose state with obstruction of upper respiratory pathways as the result of swallowing the tongue, aspiration of vomited material, acute bronchorrhea and salivation; b) in disturbances of respiration of central origin; c) in acidoses.

2. Syndrome of disturbance of hemodynamics encountered in a) collapse; b) pulmonary edema; c) hypotonia; d) burn shock.

3. Acute renal insufficiency arises in cases of poisoning by antifreeze, bichloride of mercury, dichloroethane, carbon tetrachloride and other nephrotoxic poisons, as well as in prolonged and deep collapse against a background of other intoxications.

4. Acute hepatic insufficiency as a manifestation of acute toxic hepatitis develops in cases of poisoning by dichloroethane, carbon tetrachloride, certain plant poisons (male fern, mushrooms) and medicines (mepacrine).

The four syndromes listed above for poisoning by no means include all of the possible manifestations of serious acute intoxication. Table 26 is an attempt to systematize the types of poisoning described in various literature

sources in order to put together a more complete picture of the possible pathogenetic mechanisms of the action of numerous poisons. Some of the syndromes listed in Table 26 must be viewed in more detail. In particular, we are most interested in clarifying the pathogenetic mechanisms of such syndromes as toxic edema of the lungs, hypoxia, acute insufficiency of the kidneys and liver.

Toxic Pulmonary Edema.

The caustic effect of certain toxic agents and industrial gases (nitrous oxide, ammonia) on the lungs causes the development of pulmonary edema. In particularly serious cases, the toxic edema itself is an extremal state. Thus, acute poisoning by phosgene or diphosgene with an unfavorable trend can lead to the development of pulmonary edema of extreme intensity when the victim literally chokes on the edematous fluid. In all these cases, pulmonary edema involves development of pulmonary hypoxia which can lead to a comatose (blue type of anoxemia) or collaptoid (gray type of anoxemia) state.

In the pathogenesis of toxic pulmonary edema an important role is played by disruption of permeability of pulmonary capillaries and alveoli, leading to loss of plasma into the lumina of the alveoli. Among the mechanisms which form the basis for the disruption of permeability, particular significance attaches to the nervous system. The effect of total irritation of the surface of the alveoli plays a role of a triggering mechanism; the interoceptive impulses travel along the afferent fibers to the center of the vagus nerve and include physiological mechanisms which regulate water exchange in the lungs (with involvement of the hypophysis). At the same time, the trophic function of the nervous system is disrupted as well, particularly in the injured organ. Participation of cholinergic and adrenergic mechanisms in the pathogenesis of toxic pulmonary edema at the present time can be considered proven. In addition to the reflex /280 mechanisms, the basis for the disturbance of permeability is the physical--chemical changes caused by the formation of substances in the pulmonary tissue which are capable of retaining water in the pulmonary tissue. Such substances include, for example, diphosgene ether of cholesterin according to Kling (1933).

Hence, the principal role in the pathogenesis of toxic pulmonary edema is played by the neuroreflex and biochemical mechanisms. As far as the

indirect (caustic) effect of poisons on vessels and pulmonary alveoli is concerned, they are important primarily in the case of action of high concentrations when extensive destructive disturbances occur in which protective mechanisms are unable to make themselves felt.

Hypoxic Syndrome.

Hypoxia is the most frequent pathological state which accompanies serious poisonings of various kinds and leads to coma (hypoxic coma).

The following types of toxic hypoxia can be distinguished:

1) central hypoxia, whose basis is the action of the poison on the respiratory center (narcotics of the opium group);

2) pulmonary hypoxia, whose basis is the disabling by the poison of the respiratory surface of the lungs (irritating and caustic gases and vapors);

3) hemic hypoxia, whose basis is a reduction of the amount of hemoglobin (hemolytic poisons) or destruction of their ability to carry oxygen due to its conversion into an inactive form (carboxyhemoglobin, metahemoglobin);

4) hypoxia of the tissues (histotoxic), whose basis is inhibition or paralysis of tissue respiratory processes (cyanides, hydrogen sulfide). Hypoxias can also be expanded to include peripheral hypoxia due to paralysis of respiratory muscles (curare-like substances).

These hypoxias have possible variations in their development due to the direct influence of poisons upon the respiratory function.

For a more complete analysis of the phenomenon, we must also take into account those types of hypoxia which are unrelated to the direct changes in respiratory function of the organism, but also are manifested by poisonous substances. We are speaking of hypoxias produced by disruption of the activity of the cardiovascular system (circulatory hypoxia). Circulatory hypoxia can arise as the consequence of influence of poisons upon the heart, vessels, and vasomotor center. Figure 57 shows a very complete diagram of the toxic hypoxias. It is necessary to point out that like any diagram this classification has a relative nature and does not cover all of the complex aspects of the

interrelationships between the various types of hypoxia. In practice, it is difficult to isolate any one type of hypoxia, since usually others are associated with that type. Thus, respiratory anoxia as a rule is made more serious by circulatory problems. The same is true of hemic and tissue hypoxia. Circulatory hypoxia in turn leads to disturbances of respiration (pulmonary edema). Vicious hypoxic circles gradually include other regions. This takes place in the reflex and metabolic disturbances of the microcirculation, leading to a disruption of the function of various organs and systems. Thus, when the oxygen saturation of the arterial blood drops to 50-60%, there is a narrowing of the minor vessels of the portal branch of the liver (Demling et al., 1951), a decrease in the abdominal circulation of the blood and particularly an influx along the hepatic artery (Fischer, 1959, 1960, 1961; Hara et al., 1960). All of this leads to hypoxia of the tissues of the liver and dystrophic changes.

However, as complicated as the pathogenesis of toxic hypoxia may seem to us, it is necessary in each individual case (depending on the point of application of the action of the poison) to isolate the primary mechanism for the development of hypoxia, and we hope that this diagram can facilitate the problem. Hypoxia is a universal syndrome in poisonings of different etiology. It impresses a characteristic impression on the clinical picture of poisoning and leads to the development of a number of syndromes and states (spasms, comatose states and the like). /281

Nephrotic Syndrome.

As the result of the direct nephrotoxic action of poisonous substances, and also as the result of acute insufficiency of renal circulation, this syndrome may develop. The latter may be caused by a number of factors: disturbance of general blood circulation (cardiac and vascular poisons), shock (in chemical burns, medicinal anaphyllaxis), hemolysis (under the influence of hemolytic poisons). The most serious manifestation of the nephrotoxic effect is acute renal insufficiency, which arises due to necrosis of the tubules.

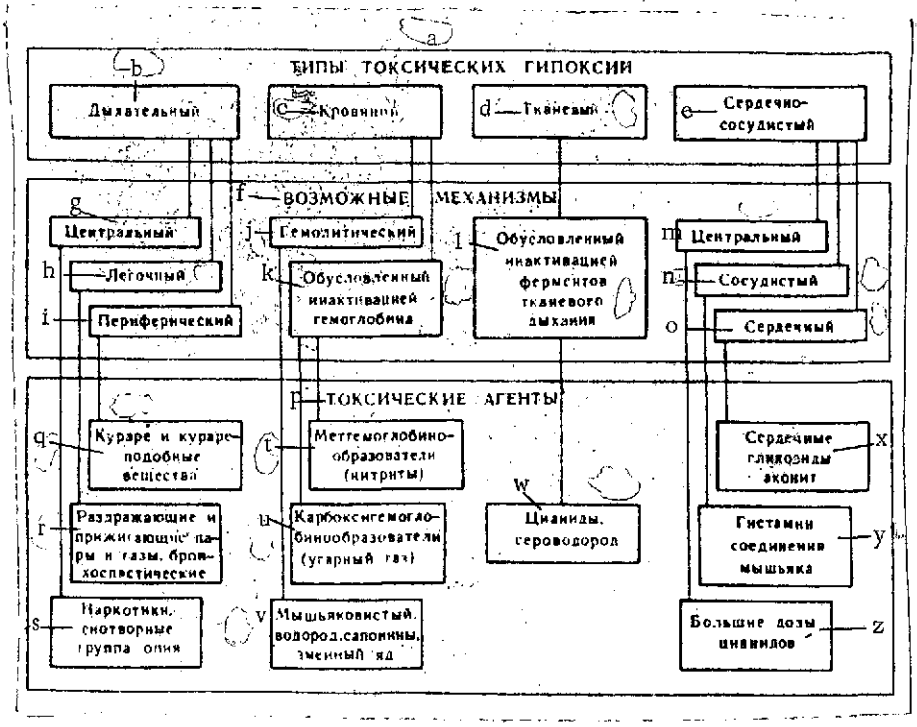

Figure 57. Types of Toxic Hypoxia. a, Types of toxic hypoxia; b, Respiratory; c, Blood; d, Tissue; e, Cardiovascular; f, Possible mechanisms; g, Central; h, Pulmonary; i, Peripheral; j, Hemolytic; k, Caused by inactivation of hemoglobin; l, Caused by inactivation of tissue respiration enzymes; m, Central; n, Vascular; o, Cardiac; p, Toxic agents; q, Curare and curare-like substances; r, Irritating and burning vapors and gases, bronchospastic; s, Narcotics, soporifics, opium group; t, Metahemoglobin formers (nitrites); u, Carboxyhemoglobin formers (carbon monoxide gas); v, Hydrogen arsenide, saponins, snake venom; w, Cyanides, hydrogen sulfide; x, Cardiac glycosides, aconite; y, Histamine compounds of arsenic; z, Large doses of cyanides.

Depending on its chemical nature, a poison can be accumulated in various parts of the proximal tubule. This explains the localization of the necrotic areas. Bichromates damage primarily the upper third, while uranium salts attack the middle third and mercury compounds, carbon tetrachloride and certain mushroom poisons (phaloidine attack the lower third of the proximal tubule. The extensive damage to the tubule with involvement of all segments is produced by the amides of sulfonic acid, propylene glycol, arsines, Berthollet's fluid and sulfanilamides (Ye. M. Tareyev, 1961). Nephrotic substances are other inorganic substances (salts of copper, cadmium, chromium, lead, hydrochloric and

/282

phosphoric acids) as well as certain organic acids (acetic and bile). Many of these substances act not only on the kidneys but also on other organs, so that one must keep in mind the possibility of including them not only among the nephrotoxic substances but also other groups of poisonous compounds. Carbon tetrachloride has a profound narcotic effect while mushroom poisons have a cholinergic action and arsines have a hemolytic one, and so forth. However, their pronounced nephrotoxicity, retained in any method of administration of the substance and independent of the manifestation of an effect on other organs and systems, makes it possible to view them as nephrotoxic compounds.

The nephrotoxic syndrome in some cases may form the basis for pathogenesis of an extremal state (uremic coma, shock in sublimated kidney).

The Syndrome of Acute Toxic Damage to the Liver.

Among the substances which have a toxic effect upon liver tissue are trinitrotoluene, dinitrophenol, dichloroethane, carbon tetrachloride, chloroform, atophane, aminazine, para-aminosalicylic acid and others. The "classic" liver poison isuusually considered to be carbon tetrachloride (CCl_4) (Drill, 1952). Until recently, the mechanism of the destructive changes in the liver was viewed exclusively as the consequence of the direct damaging effect of the poison upon the liver cells. However, in the development of necroses an equally important role is evidently played by disturbances of the microcirculation. This is indicated by the fact that the most pronounced damage is observed at the center of the lobes (centrilobular necrosis), which takes the form of particularly unfavorable conditions of blood supply as the result of suppression of the venules and sinusoids of the edematous tissue of the liver — a secondary ischemia (Fischer, 1961). A sharp drop in the renal blood circulation is observed in studies of the index of purification of the liver (Saragea, Barbu, 1961). An increase in the resistance of the portal branch of the liver is indicated by a rise in the pressure gradient between the portal vein and its terminal hepatic branches (Brauer, 1961).

At the present time it is felt that the origin of toxic dystrophies of the liver involve two factors: primary poisoning of the cells by the poison and secondary ischemia. In certain cases clinicists speak of hepato-renal syndrome (simultaneous toxic damage to the liver and kidneys).

Mechanism of Action of Poisons.

The view of modern physiology concerning the organism as a single auto-regulatory system makes it possible to view the action of poisonous substances as extreme stimulants of the environment. I. P. Pavlov wrote: "...Many substances administered to the organism disturb its equilibrium due to certain relationships to the peripheral nervous endings and a primarily sensitive easily reaction part of the animal body." This is particularly true of substances that have an irritating or caustic type of effect, which, due to their influence upon the receptors, cause numerous pathological reflex reactions (spasms of the bronchial musculature under the influence of irritating gases and vapors, vomiting with various oral poisons and so forth). However, the influence of poisons upon the nerve endings characterizes only one pathogenetic mechanism of their action. Many substances have a direct effect upon /283 organs and tissues. The effect of a poisonous substance upon any tissue must be viewed as the result of its intervention in tissue biochemical processes. The object of this action may be any tissue, any organ. However, the higher the state of differentiation of the tissue, the more complex and diverse are the processes occurring in it and the greater the possibility of a pharmacological intervention in the function of such tissues, and consequently the higher the sensitivity of this tissue to its action. High sensitivity to direct action of toxic agents is shown by the central nervous system. A great many neurotropic substances are known which have a primary effect upon certain areas of the nervous system, taking the form of a disruption of the reflex influences involving various levels of the central nervous system. Of course we must keep in mind that poisonous substances can have a central effect not only due to their direct action upon the brain centers but also through irritation or inhibition of the activating systems of the brain (reticular formation and so forth). Generally speaking, a strictly selective action of poisonous and medicinal substances upon concrete centers in the brain has a rather problematical nature. Obviously, it would be more correct to speak not of a local influence of a substance upon a center but upon the levels of its intervention in the regulation of the physiological processes. In this connection, together with a "specific" method of influence of a substance upon a certain morphofunctional substrate of

a system, regulating a given function, we must take into account the possibility of influence of a given substance by a "nonspecific" pathway. The latter boils down to a change in the tonic activity of the primary, or effector, elements of the neurogenic regulation due to an increase or weakening of modulating influences of stressed structures and the general level of afferentation, coming to a given neuron (A. V. Val'dman, 1969). The object of their selective action of a great many poisons is also the effector nerve pathways, particularly at points of transmission of nerve impulses from one neuron to another (cholinergic, anticholinesterase and adrenergic substances, previously listed among the vegetative poisons). This group of substances also includes modern toxic agents with a neuroparalytic effect (zarin, zoman and V-gases). However, at the present time the concept of the mechanism of action of this group of poisons also includes correctives since it has been found that many of these substances, together with their action on the region of the endings of the centrifugal nerves, have an influence on the cholino- and adrenergic systems of the brain, with this effect in certain representatives even being greater than the peripheral effects.

For certain poisonous substances, the object of the direct action is the tissue of the functioning organs. Thus, the glycosides are selectively poisonous to the muscles of the heart, the alkaloids of ergot - for muscles of the uterus, alloxan (a derivative of pyrimidine) for the spleen (its internal secretory apparatus).

The effect of poisons upon any organ or tissue is based upon intervention in the biochemical processes which ensure the function of that organ or system. This influence lies in the very nature of the poisons, whose chemical structure may resemble that of natural metabolites. Consequently, as the result of this similarity there is an intervention of the exogenic toxic agent in the metabloic processes of the organism, leading to their destruction. One could list a great many examples which illustrate this important view, necessary to understanding the mechanism of action of poisons. We shall merely limit ourselves to several of the most striking ones. Cinnamic /?/ acid is one of the strongest poisons; it paralyzes the cell respiration, blocking the iron-containing enzyme called respiratory enzyme (cytochromoxidase). Prvssie acid reacts with the oxidized form of cytochromoxidase, forming a complex compound with its iron, and this

destroys its catalytic function in the reaction of aerobic oxidation of cytochrom C, ie., the transport of electrons from the reduced cytochrome C to the exygen.

The action of the arsenic compounds and heavy metals is explained by their interaction with the sulfhydryl groups of enzymes. Thus, poisonous compounds of arsenic, including lewisite, form strong complexes with thiol groups of enzymes. The most selective influence is produced by these substances upon the enzyme pyruvatoxidase, more exactly, dihydrolipoic acid which enters into its composition (Peters, 1952).

This discovery made it possible to propose as effective antidotes to compounds of arsenic and heavy metals, dithiols which, "taking the attack upon themselves" of the poison and binding the latter, protect the SH-groups of the vitally important enzyme. The biochemical mechanism of the toxic action of modern toxic agents with a neuroparalytic action consists in blockage of the active groups of enzymes of acetylcholinesterase, so that the synaptic transmission is interrupted in the central and peripheral nervous system. Reactivation of the enzyme by preparations from the oxime group causes restoration of this process.

Of course, we must recognize that biochemical mechanisms have been discovered for only a small number of poisons. Among modern toxicologists, there are important problems to be solved in conjunction with these mechanisms for the purpose of developing more effective antidotes. It is equally important to study the pathophysiology of the toxic process necessary for an understanding of the pathogenesis of intoxication and for finding means of pathogenetic therapy.

Methods of Prevention and Treatment of Poisoning.

The prevention of poisoning constitutes one of the most important problems in modern toxicology. It consists primarily in eliminating those conditions which can lead to poisoning in industry and in the home. Under industrial conditions this is work with chemically harmful substances in protective clothing and observation of all other rules for safety measures: systematic sanitary examinations of the concentrations of chemically harmful substances in the air

of working environments (they must not exceed the MAC [maximum allowable concentration]), technical correctness of operation of apparatus and so forth; in the home there must be competent and proper usage of medications, poisonous chemicals and other objects of domestic chemistry. It is particularly important to protect children against possible poisoning by objects of domestic chemistry and medicines (according to the statistics, the greatest percentages of poisoning occur among young children). All of these and other hygienic and sanitary-educational measures in the ideal case may lead to total elimination of poisoning. However, this is not the case in practice. Clinical toxicology has materials available which indicate that industrial and residential poisonings are encountered quite frequently and that problems of prevention and therapy of poisoning not only do not lose their significance but become even more timely in conjunction with the unusually intensive penetration of chemistry into production and the home. It is also necessary to remember that the most poisonous compounds in some of the NATO countries are included among the substances used for massive attacks on people. The energetic struggle with /285
poisoning usually begins with a delay when the symptoms of poisoning are still developing in the person. Frequently victims are brought to the hospital in a serious condition when the time for inactivating the poison has already passed. It is desirable to start the fight against intoxication immediately after contact of the person with the poison, when the symptoms of its resorptive action have not yet made themselves felt.

Measures used for the treatment of poisoning for the purpose of inactivating the poison and eliminating the pathological disturbances produced by it (antidote) can be used prior to intake of the poison and after its resorption. The former include antidotes that bind or neutralize the poison in the stomach or on the skin or mucous membranes while the second consists of substances which disarm the poison in the blood and biochemical systems or the organism, and also counteract the toxic effects due to physiological antagonism. Neutralizing unabsorbed poison can be carried out by absorption or chemical interaction with subsequent elimination from the organism. Activated charcoal, magnesium oxide (or some other neutralizer of poison depending on its nature) and tanwin are used for these purposes; the latter possesses the property to bind alkaloids and heavy metals. The use of antidotes of this kind must be combined

with the adoption of all measures aimed at eliminating the unabsorbed poison (copious drinking, washing out of the stomach, vomiting). While doing this it is desirable to use substances to wash out the stomach which neutralize the poison. Thus, in cases of acid poisoning one can achieve their neutralization by giving internally mild solutions of alkali. In order to neutralize alkalis on the other hand one uses dilute weak acids (citric, acetic). In cases of poisoning by salts of heavy metals and arsenic, antidotum metallorum is given internally, which changes them to insoluble sulfides. In cases of poisoning by the above poisons it is useful to give internally milk or egg white, which form albuminates with these poisons (arsenic is an exception). Some poisons (for example, morphine) are neutralized by the action of oxidation. For this purpose, potassium permanganate is used.

In the course of treatment of poisoning, it is rarely possible to completely neutralize the poison prior to its absorption. Therefore, it becomes necessary to use immediately antidotes with a resorptive action. The poison in the blood in some cases can be neutralized by using chemical antidotes. Thus, unithiol neutralizes arsenic and mercury. Methylene blue forms a compound with hemoglobin (metahemoglobin) which neutralizes strong acid. Some oximes possess the ability to neutralize organophosphoric anticholinesterase poisons.

The use of chemical antidotes is effective only in the initial period of intoxication, when the poison still has not interacted with the biochemical systems of the organism participating in the regulation of vitally important organism functions. In this connection, their use is limited with respect to time. Moreover, the quantity of chemical antidotes is small and, relative to the majority of poisons, toxicology does not have such specific means available. For these reasons, those antidotes are most popular whose action is directed not at the poison but at the toxic effect it produces. The basis for the antidote action of such substances is the concurrent relationships between the antidotes and the poison in the action upon biochemical systems of the organism as the result of which the antidote draws out the toxic compound from these systems and thereby restores their normal function. This principle forms the basis of the therapeutic action of oxygen in cases of carbon monoxide poisoning; the /286
antidotal effect of atropine in cases of poisoning by muscarine and similar

compounds, anticholinesterase substances in cases of poisoning by curare-like substances the concurrent-blocking action of reactivators of cholinesterase in cases of poisoning by organophosphoric poisons of the zarin type, and so forth. The action of such antidotes is selective and therefore particularly effective.

However, the concurrent relationships between the poison and the antidote in the action on the biochemical systems characterize only one of the variants of the antidote action. Much more frequently, we are speaking of a functional antagonism when the antidote acts upon the organism in the opposite way, in contrast to the poison or indirectly counteracts the toxic effect acting on systems which are not damaged directly by the poison but which participate in the regulation of the activity of the damaged system. Thus, in toxic pulmonary edema the therapeutic effect is caused by cardiac substances which promote the improvement of circulation in the pulmonary circulation. In this sense the symptomatic methods may play the role of functional antidotes. An important element in the pathogenetic therapy of poisoning is stimulation of the antidotal functions of the liver through increasing the glycogen content (intravenous administration of glucose solutions).

Speeding up the excretion of poisons is also one of the ways of treating poisoning. In the case of gases and vapors it is artificial respiration (stimulating the function of respiration); intensification of the renal excretory processes is achieved by copious drinking, cardiac and diuretic substances. In cases of injury by poison to the kidneys particular significance attaches to repeated paranephral novocaine block and operative methods of treatment: hemodialysis (particularly in the cases when hyperkaliemia develops), peritonal dialysis, and replacement of the blood by transfusion (O. S. Glozman, A. P. Kasatkina, 1959).

Methods of pathogenetic therapy of extremal states, caused by poisons, largely coincide with the treatment of analogous states of other etiology. However, they have one important theoretical feature: regardless of the clinical state causing the poisoning and regardless of the means employed by the physician to try to bring the patient out of this state, he must always remember the need for using substances with a specific and pathogenetic therapy, together with

certain symptomatic means. Thus, for example, in the treatment of the comatose state produced by atropine (atropine coma), it is far from a matter of indifference whether or not the preparations usually employed in the treatment of comatose states will be employed or physostigmine, which is a concurrent antagonist of atropine. According to the data of Forrer and Miller (1958), the administration of 30 to 200 mg of atropine in man causes coma which lasts 4-6 hours. This state is rapidly overcome by physostigmine at a dose of 4 mg given I.V. Here is another example. Organophosphoric poisons cause a deep, difficult to overcome coma. Bringing a person out of such a state can only be accomplished by using a specific antidote, dipyroxime (TMB-4) whose active mechanism consists in the reactivation of cholinesterase blocked by the poison (Ye. A. Luzhnikov, 1968).

In the course of treating poisons it is necessary to take into account other features as well. These include in particular the greater reversibility of the toxic extremal state in comparison with similar states of different etiology. In particular, this is true of the toxic coma. Thus, we know that in cases of poisoning by barbiturates, aminazine, atropine, anticholinesterase and other substances a man may keep his compensatory mechanisms at a high level for a long time while in a comatose state. This makes it possible, even at /287
comparatively late periods of intervention, to rescue a poisoned person under conditions of complex utilization of methods of antidote, pathogenetic and symptomatic therapy.

A dangerous symptom of poisoning by poisons which inhibit the central nervous system is insufficiency of respiration. In this connection it has been shown that the use of analeptics (corazole, cordiamine, cytitone can be valuable). Recently, it has been found that a particularly effective analeptic is etimizol, which is similar in structure to caffeine (S. V. Anichkov, Yu. S. Borodkin, 1959). In cases of poisoning by narcotic and soporific substances, the most effective analeptic is bemegrid. If the use of analeptics does not have an effect, it is necessary to use artificial respiratory apparatus (with intubation or tracheotomy). The struggle against shock becomes primarily one of eliminating the chemical irritant, using neuroplegic substances and ensuring maximum rest. Later, measures are used to prevent acute insufficiency of the cardiovascular system and respiration. The therapy for collapse depends upon

the cause. In cases of difficulty in determining the type of collapse, therapy is based on general principles (cardiovascular and respiratory analeptics, noradrenaline, intravenous transfusion of blood plasma and plasma substitute fluids). In order to eliminate cardiac weakness, the most effective thing is intravenous administration of strophantine. In order to prevent or treat toxic pulmonary edema it is necessary to take a number of measures: blood transfusion (in cases of incipient edema), oxygen therapy, carbogen therapy (in the gray type of asphyxia and CO poisoning), cardiovascular agents (adrenaline is counterindicated), calcium preparations (intravenously), ganglioblockers (for example benzohexonium). Hypoxic states require organization of oxygen therapy under conditions of reduced utilization of oxygen by the organism combined with means of improving respiration and circulation. It is also possible to consider the use of agents which reduce the consumption of oxygen by the tissues. In treatment of toxic hypoxia, as in the treatment of other states caused by poisoning, it is necessary to use the possibilities of antidote therapy (metahemoglobin formers in poisoning by cyanides).

It is necessary to take into account the possibility of medicinal influences upon the course of metabolic processes in the tissues, particularly in the heart muscle (ATP, cocarboxylase, vitamins of the B and C group). In order to prevent hepatic insufficiency, it is recommended that large amounts of glucose be given in conjunction with insulin, vitamins, calcium preparations, methionine and campolon.

When acute renal insufficiency develops (poisoning by bichlonde of mercury carbon tetrachloride, dichloroethane and so forth) it is necessary to have intravenous administration of glucose with ascorbic acid, sodium chloride (with extensive vomiting), sodium bicarbonate (in acidosis), cross transfusion of blood, hemodialysis, or an artificial kidney. In hematuria, vitamin K is indicated. In order to eliminate the sharp painful syndrome, preparations made of morphine, promedol, atropine, magnesium sulfate, papaverine, aprophene, and vitamin B_1 are recommended. In addition, in certain cases novacaine block around the kidney is used. The spasmatic syndrome is eliminated by breathing oxygen (in the asphyxic state), chloral hydrate, hexanal, barbamyl, and magnesium sulfate. Morphine is counterindicated.

The therapy of other toxic states (see Table 29) is carried out in accordance with the general principles of therapy under conditions of usage of methods of antidote therapy in those cases when this is possible. The weakening of protective forces of the organism by the poison, particularly in conjunction with the extremal state which has been withstood, requires rational use of the entire arsenal of therapeutic measures aimed at restoration of the functions of the organism and prevent of secondary infection. /288

Conclusion.

The pathophysiology of extremal states created by exogenic intoxicators is one of the least developed areas of experimental and clinical toxicology. In clinical practice, little attention is paid to the characteristics of the development and the course of these states in cases of poisoning, so that their treatment frequently is of a routine nature and is insufficiently effective. Moreover, it is far from a matter of indifference what toxic agent caused the poisoning, and what concrete pathogenetic mechanisms led to the development of the extremal state.

In this chapter we have attempted to classify poisons with an eye toward particularly typical pathological syndromes. This has enabled us to view the latter not only on the level of clinical-toxicological characteristics of the condition itself, but also in conjunction with those pathogenetic mechanisms which form the basis of their development. These mechanisms unfortunately have not been fully divulged; the key to the understanding of the essence of the development of pathological processes, the selection and development of methods of pathogenetic therapy. There is another way of understanding these phenomena: the decipherment of biochemical (molecular) mechanisms of action of poisons. However, this aspect of the problem must be the subject of a special study.

In examining the characteristics of the action of various poisons, we are struck by the extreme diversity of their manifestations, the possibility of direct or indirect intervention of the poison in the functional aspects of any physiological system, and its various branches. It is natural that a total coverage of these phenomena within the scope of the present chapter would be impossible, and it would hardly be advantageous to burden the presentation of

this problem by listing the groups of poisons and the individual compounds (their numbers reach several thousand) together with a description of numerous symptoms of the poisoning. We saw our problem in another light — the discovery of the numerous, most typical pathogenetic mechanisms of the action of poisons leading finally to the development of an extremal state, and in connection with this, determining the theoretical trends for therapy. It is precisely this approach which seems to us most fruitful for working out a uniform approach toward understanding the pathophysiological nature of poisoning.

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